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Focused Management of Patients with Severe Acute Brain Injury and ARDS

Running head: Focused management of severe brain injury and ARDS

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Abbreviations

ARDS=acute respiratory distress syndrome, BAL=bronchoalveolar lavage, BP=blood pressure, CPP=cerebral perfusion pressure, CSF=cerebral spinal fluid, ECMO= extracorporeal membrane oxygenation, EEG=electroencephalography, EVD=external ventricular drain, GCS=Glasgow coma scale, HD=hospital day, ICH=intracranial hemorrhage, ICP=intracranial pressure, IH=intracranial hypertension, LTVMV=low tidal volume mechanical ventilation, MAP=mean arterial pressure, MVC=motor vehicle accident, PEEP=positive end-expiratory pressure, PMH=past-medical history, PSH=paroxysmal sympathetic hyperactivity, RASS=Richmond Agitation Sedation Scale, sABI=severe acute brain injury, SAH=subarachnoid hemorrhage, SDH=subdural hematoma, TBI=traumatic brain injury, TRALI=transfusion related acute lung injury

Abstract:

Considering the COVID-19 pandemic where concomitant occurrence of acute respiratory distress syndrome (ARDS) and severe acute brain injury (sABI) has increasingly co-emerged, we synthesize existing data regarding the simultaneous management of both conditions. Our aim is to provide readers with fundamental principles and concepts for the management of sABI and ARDS, and highlight challenges and conflicts encountered while managing concurrent disease. Up to 40 percent of patients with sABI can develop ARDS. While there are trials and guidelines to support the mainstays of treatment for ARDS and sABI independently, guidance on concomitant management is limited. Treatment strategies aimed at managing severe ARDS may at times conflict with the management of sABI. In this narrative review, we discuss the physiological basis and risks involved during simultaneous management of ARDS and sABI, summarize evidence for treatment decisions, and demonstrate these principles using hypothetical case scenarios. Use of invasive or non-invasive monitoring to assess brain and lung physiology may facilitate goal-directed treatment strategies with the potential to improve outcome. Understanding the pathophysiology and key treatment concepts for co-management of these conditions is critical to optimizing care in this high-acuity patient population.

Introduction

Acute respiratory distress syndrome (ARDS) occurs in up to 40% patients (1, 2) with severe acute brain injury (sABI), including acute ischemic stroke (AIS), subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), and traumatic brain injury (TBI), and is a major determinant of morbidity and mortality(1, 3). With the increase in ARDS cases and reports of neurological complications in COVID-19(4, 5), there is an increasing need to manage concomitant severe ARDS and sABI. Standard treatment strategies for ARDS can conflict with management of elevated intracranial pressure (ICP) and reduced cerebral perfusion pressure (CPP). Here, we introduce evidence-based independent management of ARDS and sABI, then review challenges of concurrent management highlighting case scenarios with extrapolation of evidence-based management recommendations.

Methods

PubMed and Google Scholar were searched using ARDS and X, with X representing sABI (e.g., ICP, hemorrhage, stroke, traumatic brain injury) and included references known to authors. Abstracts were reviewed, and articles whose abstracts addressed ARDS and/or neurocritical care were evaluated in full. A minimum of 210 articles were reviewed in full, with 113 articles (1973-2021) ultimately deemed relevant for inclusion.

Management of the brain-lung conflict

sABIcan induce and worsen ARDS via multiple physiologic pathways (Figure 1). Many ARDS therapies can raise ICP or decrease CPP, potentiating secondary brain injury due to impaired cerebral autoregulation. In patients with concurrent ARDS-sABI, oxygenation, ventilation, and perfusion parameters considered standard ARDS-care may insufficiently support the injured, hypermetabolic brain. Many ARDS studies excluded patients with sABI and thus do not consider the physiologic implications of ARDS management in sABI patients. Some strategies for

optimizing brain and lung physiology conflict and, hence, nuanced management strategies are necessary(6) (Figure 2). Here we discuss theoretic risks, evidence-based treatment considerations and propose management strategies extrapolated from existing data and expert opinion (Table 1).

Low tidal volume mechanical ventilation (LTVMV)

Challenge*: LTVMV improves mortality in ARDS, but may cause hypercarbia and hypoxemia, which may lead to raised ICP and brain hypoxia.*

Physiology

High tidal volumes are associated with ARDS development during mechanical ventilation (odds ratio 1.3 per ml >6ml/kg)(7–10). The ARMA trial demonstrated that ventilation with low tidal volumes (4-6mL/kg ideal body weight) led to a 9% absolute reduction in mortality(11) and LTVMV has shown to increase ventilator-free days (11, 12). LTVMV targets are often PaO2 of 55–80mmHg(11, 13) and pH >7.15, with permissive hypercapnia.

Theoretical risk in sABI:

ARDS protocols often allow hypercapnia and mild hypoxemia, but the resulting cerebral arteriole vasodilation and increased ICP, as well as brain tissue hypoxia, is poorly tolerated after sABI. Cerebral vasculature is highly responsive to carbon dioxide levels. Increasing arterial carbon dioxide tension (P_aCO_2)—as permitted in LTVMV—can lead to hypercapnia, cerebral vasodilation, and a rise in ICP. In contrast, hyperventilation can decrease P_aCO_2 and induce alkalemia and transient ICP reduction. However, this occurs via cerebral arteriole vasoconstriction (14), which may worsen cerebral ischemia.

Evidence:

Evidence supports hypercapnia-induced cerebral vasodilation and increased ICP(15). However, prolonged *hypo*capnia (P_aCO_2<25mmHg for >30 minutes) is also no longer recommended (16).

Hyperventilation should only be a temporizing measure (<30 min) while awaiting definitive intracranial hypertension (IH) treatment(16, 17) to avoid cerebral ischemia(17). Thus, a target P_aCO_2 of 35-45mmHg or a graded hypoventilation strategy is recommended(18). Though mild hypoxemia and is well-tolerated in patients without brain injury, sABI patients have up to a 50% higher odds of death with a PaO2 < 110 mm Hg(19–21).

Summary:

The benefit of LTVMV must be balanced with risks of hypercarbia and hypoxemia. An individualized target, based on direct measures of brain physiology such as invasive ICP and brain tissue oxygen monitoring should be implemented(11, 22, 23). If direct measurement is not feasible, normal P_aCO_2 (35-45mmHg) and P_aO2 >110 mmHg should be targeted as much as tolerated from a lung compliance standpoint.

<u>High Positive End Expiratory Pressure (PEEP)</u>

***Challenge**:* High PEEP may improve oxygenation but reduce cerebral perfusion by raising ICP.

Physiology

PEEP prevents alveolar collapse to maintain oxygenation, increases functional residual capacity and improves ventilation-perfusion matching (24–26). PEEP may be optimized to individual patient physiology via: 1) empiric PEEP and F_IO_2 titration tables, 2) pressure-volume loops or other dynamic physiologic parameters, 3) esophageal manometry to estimate transpulmonary pressure, 4) titration of PEEP to optimize driving pressure(27). Lower driving pressure is associated with reduced mortality(28).

Theoretical risk in sABI:

PEEP increases intrathoracic pressure which can increase right atrial pressure and decrease cerebral venous drainage resulting in elevated ICP(24–26, 29–32). PEEP may trigger compensatory vasodilation, thereby increasing ICP when cerebral autoregulation is intact and

intracranial compliance is decreased. Conversely, if cerebral autoregulation is impaired, increased PEEP may reduce cerebral perfusion pressure causing cerebral ischemia (33–35).

Evidence:

In a trial assessing the effect of PEEP on cerebral autoregulation in ARDS patients without known sABI (24), ≥50% of patients had impaired cerebral autoregulation with increased PEEP, but no clinical significance was seen at PEEP<14cmH20(24). Studies in sABI reveal conflicting opinions regarding the theoretical concerns of IH with increased PEEP(35, 36). Studies in SAH, AIS and TBI have shown that increasing PEEP up to 12cmH20 had no significant change on ICP(37–39). However, systemic and cerebral hemodynamics may be more dramatically affected by changes in PEEP in patients with high respiratory system compliance compared to patients with low compliance(37).

Summary:

High PEEP carries a theoretical risk of worsening ICP, but the effect is minimal when PEEP is ≤12cmH20 and in patients with low respiratory system compliance. Adequate volume resuscitation along with high PEEP may mitigate adverse effects (39). A recent consensus panel (40) recommended using the same PEEP in sABI patients as in non-brain injured patients, unless IH was noted to be linked to increased PEEP. ICP monitoring in sABI-ARDS patients may aid in PEEP titration. Oxygenation targets can be titrated to brain tissue oxygen measures or targeted to a P_aO2 >110 mmHg, as tolerated based on lung compliance, if monitoring is not possible.

Recruitment maneuvers

Challenge*: Recruitment maneuvers may open collapsed alveoli and improve oxygenation but can cause hypotension and impair brain perfusion.*

Physiology

Recruitment maneuvers open collapsed alveoli using sustained or stepwise increase/decrease inflation for a short duration. A randomized trial found that aggressive recruitment maneuvers followed by high PEEP increased mortality, hemodynamic collapse, and barotrauma in ARDS(41).

Theoretical risk in sABI:

Sudden high distending pressures used with recruitment maneuvers can be hazardous for systemic and cerebral hemodynamics.

Evidence:

Evidence supports that recruitment maneuvers (20-35cmH20) may significantly decrease CPP and elevate ICP (42, 43). Modified pressure controlled recruitment maneuvers may be tolerated in sABI patients without baseline IH(42).

Summary:

Recruitment maneuvers using PEEP ≥20cmH20 should be avoided when maintaining cerebral perfusion is of critical importance, or ICP control is a major concern.

Pulmonary vasodilator therapy

***Challenge**:* Inhaled pulmonary vasodilators may improve ventilation-perfusion matching and hypoxemia but could inhibit platelet function.

Physiology:

Inhaled vasodilators selectively dilate pulmonary capillaries in well ventilated alveoli to improve ventilation/perfusion matching and oxygenation.

Theoretical risk in sABI:

Pulmonary vasodilators are well-tolerated in sABI patients, likely from improved cerebral oxygenation(44). One theoretical complication of prostacyclins is an inhibitory impact on platelet function and/or synergism with P2Y12 inhibitors(45, 46).

Evidence:

Case reports and studies suggest pulmonary vasodilators may improve ICP and cerebral oxygenation(47–50). Potential complications include hypotension if systemically absorbed, and bleeding due to platelet inhibition(26).

Summary:

Limited evidence suggests pulmonary vasodilators are safe and potentially beneficial in sABI and ARDS. The minor concern of antiplatelet effects has yet to be validated and should be weighed based on bleeding risks in the individual patients.

Fluid management

***Challenge**:* A fluid conservative strategy reduces duration of ventilation in ARDS, but hypovolemia may reduce cerebral perfusion and aggressive hyperosmolar therapy may induce hypervolemia.

Physiology

Hyperosmolar therapy (HT)—e.g., mannitol or hypertonic saline - is the standard treatment for intracranial hypertension (IH)(14, 51). HT induces movement of fluid from interstitial/intracellular space to intravascular space, reducing cerebral edema and ICP(52). Recent guidelines suggest favoring hypertonic saline(17), but evidence remains limited. The choice is mainly guided by factors accounting for comorbidities (e.g., heart failure, renal failure), serum values (e.g., sodium concentration, osmolality), and clinical factors (e.g., hypovolemia, central venous access).

Theoretical risk in sABI:

While aggressive diuresis is commonly recommended in ARDS, euvolemia is essential for maintaining adequate CPP after sABI. Additionally, hypertonic saline may counter diuresis efforts especially in concurrent heart failure or valvular disease and mannitol may worsen septic physiology or renal failure.

Evidence: The FACTT trial established that conservative fluid management in ARDS leads to more ventilator-free days and improved gas exchange(53). After initial resuscitation, early,

aggressive diuresis is often implemented. However, hypovolemia and resultant hypotension reduces CPP and worsens outcome after sABI(54). Similarly, hypervolemia may worsen outcomes in sABI (55, 56).

Summary: Fluid strategy should be tailored to the individual patient. Careful assessment of fluid status and judicious use of fluids and HT is critical and may be best guided by simultaneous hemodynamic and cerebral perfusion/oxygenation monitoring(57). Special considerations include avoiding hypotension in TBI and maintaining cerebral perfusion in SAH to reduce vasospasm risk.

Sedation and neuromuscular blockade

Challenge*:* Deep sedation and neuromuscular blockade (NMB) are used to improve ventilator synchrony and reduce oxygen consumption in ARDS but limits the ability to perform a neurological examination.

Physiology:

Sedation and NMB decrease global oxygen consumption, improve patient-ventilator synchrony, and optimize chest-wall viscoelasticity. However, minimizing their use reduces delirium, promotes mobility, and reduces duration of mechanical ventilation(58). While one randomized trial demonstrated improved mortality and oxygenation among patients with moderate-to-severe ARDS treated with NMB(59), the ROSE trial found no benefit in 90-day mortality(60). It did, however, demonstrate that NMB is safe, well-tolerated, and may be considered for patients with refractory hypoxemia or ventilator dysynchrony (60).

Propofol and benzodiazepines are example anesthetics used in refractory IH management. They can reduce seizures (which elevate ICP and $CMRO_2$)(61, 62). Managing pain decreases ICP elicited by Valsalva maneuver(63). Neuromuscular blockade (NMB) reduces ICP by reducing airway and intrathoracic pressure often related to biting the endotracheal tube, shivering, posturing, or breathing against the ventilator, which facilitates cerebral venous outflow. In addition, NMB reduces metabolic demand secondary to skeletal muscle contraction thus

decreasing CMRO2. Barbiturates also lower $CMRO_2$ but may reduce ICP by additional mechanisms(64).

Theoretical risk in sABI:

Loss of neurologic exam to monitor for neurological deterioration, increases risk of delirium and risk of ICU acquired weakness which further complicate neurological examination, management decision and, prognostication during lung recovery(65).

Evidence:

While the neurologic exam is critical, sABI patients with IH may have increased ICP and metabolic crisis with daily awakenings which may contribute to secondary brain injury(66, 67).

Summary:

Sedation and paralytics can improve both ICP and oxygenation in sABI and ARDS and improve ventilator dysynchrony. Their use may outweigh the risk of a temporary loss in neurologic exam. However, minimal effective dose and duration should be used to reduce hypotension, delirium and sustained loss of neurologic exam. In cases of high concern for neurologic deterioration, alternative approaches to neurological assessment, such as pupillometry, continuous EEG, surveillance CT scans or other non-invasive or invasive monitoring, may be considered in patients receiving deep sedation or neuromuscular blockade.

<u>*Steroids*</u>

Challenge*: Corticosteroids may be helpful in ARDS, especially in cases such as COVID-19, but may be harmful in some types of brain injury.*

Physiology:

Corticosteroids may reduce pulmonary and systemic inflammation in ARDS, and may have antifibrotic properties, though ARDS is a heterogenous syndrome with many etiologies and both hypoinflammatory and hyperinflammatory phenotypes(68). Corticosteroids can aid in vasogenic

edema by reducing permeability of the blood-brain-barrier, but is not effective in injuries which induce cytotoxic edema(69).

Theoretical risk in sABI:

Steroids worsen outcomes in ischemic stroke, intracranial hemorrhage, and TBI. They are also an independent risk factor for ICU acquired weakness which further complicates neurological examination and recovery in sABI(65).

Evidence:

Glucocorticoid use for cerebral edema is common and has shown benefits in brain tumors(52, 70), tuberculous and bacterial meningitis(17, 71). However, there is evidence suggesting that steroids are potentially harmful in cerebral edema associated with intracerebral hemorrhage(17), ischemic stroke(72) or traumatic brain injury (TBI)(17, 73).

Corticosteroids in ARDS are controversial, except when the etiology is COVID. A randomized trial demonstrated early administration of dexamethasone in patients with moderate-to-severe ARDS improved mortality(74, 75). However, older literature suggests late initiation (>14 days) of methylprednisolone increases mortality(76). Regarding the current COVID-19 pandemic, the use of steroids decreases mortality in patients with respiratory failure due to COVID-19 pneumonia(77, 78). While steroids may be beneficial in ARDS (74, 77, 78), steroids in multiple forms of sABI are detrimental to recovery(17, 72, 73).

Summary:

While steroids may be beneficial in ARDS, individual sABI patient risk-benefit should be considered.

Prone Positioning (PP)

Challenge*: In addition to the potential for increased ICP, there is added complexity in proning a patient with one or more intracranial drains or invasive ICP monitors.*

Physiology

PP improves gas exchange through recruitment of dependent lung regions and reduces ventilator-induced lung injury by creating more uniform ventilation(79). A meta-analysis suggested a survival benefit for severe ARDS(80), and the PROSEVA trial found a mortality benefit if PP is performed ≥16 hours per day(81). A synergistic mortality reduction was seen with PP and LTVMV. However, these trials excluded patients with sABI.

Theoretical risk in sABI:

Traditional PP can result in a significant elevation of ICP given the reduced head elevation and potential inhibition of cerebral venous drainage due to compression of neck veins(82–84). Also, invasive brain monitors (e.g. EVD) can be accidentally displaced (14, 15, 20-22, 54, 106). Because of these risks, sABI patients have been excluded from PP studies(81, 86, 87). Transient IH may occur particularly during and immediately after PP. Proper preparation by optimizing ICP prior to PP may help minimize ICP fluctuations. This includes pre-medication (hyperosmolar therapy, sedation/NMB), temperature management, and optimal CSF drainage. Once prone, use of reverse Trendelenburg to achieve head of bed elevation, and ensuring midline head positioning are simple maneuvers to help decrease ICP by improving cerebral venous return(88, 89) and CSF redistribution(90, 91). ICP-CPP balance appears optimized around 30-45°(92–94). Pillows and wedges can help with head elevation and maintenance of midline position while reducing the impact of abdominal pressure on ICP.

Evidence

There is no clear evidence of when and how long to prone sABI patients. Based on small studies, PP benefits on gas exchange and cerebral tissue oxygenation may outweigh risk of IH and CPP reduction in specific populations(95, 96). Other studies suggest that changes in ICP and CPP during proning in sABI are clinically insignificant(83, 97–99).

Summary:

While existing evidence is not strong(40), PP is a challenging but feasible option in patients with concurrent ARDS and IH. ICP monitors, via EVD or intraparenchymal monitor, are recommended

to optimize management of patients in PP. However special care planning is needed to ensure proper bedside management and prevent dislodgement of invasive brain monitors during pronation/supination. Mispositioning of the EVD system can lead to erroneous interpretation of ICPs and over- or under-drainage of CSF. In PP, reverse Trendelenburg head should be used to maintain a goal HOB elevation approximating 30°.

Alternative Strategy-Supine Chest Compression:

When PP is contraindicated, supine chest compression with the use of weights on the anterior chest wall yields similar physiological effects. Splinting of the anterior chest leads to a change in chest wall elastance and modifies regional ventilation to redistribute tidal volume and PEEP towards dependent lung regions. Dialysis (2 L saline) bags, sandbags and weight bars have been used as chest weights. While there are no evidence-based studies currently, chest weights have been used in neurointensive care units in low resource settings for years ((100), personal communication David Menon and AS). Chest weights are typically left for 8 to 12 hours initially with close monitoring to avoid pressure injury. Head of the bed position at 30 degrees is maintained to optimize ICP management. If a patient shows improving oxygenation this strategy can be continued for longer periods with periodic breaks akin to PP. An actively enrolling trial ALTERPRONE (NCT03719937) utilizes 100g/kg weight on the anterior chest wall for 3 hours in supine position and 30-degrees head up, when PP is contraindicated or not feasible. Patient with ICP more than 30 mmHg or CPP less than 60 mmHg are included.

ECMO

Challenge*:* ECMO can improve oxygenation and perhaps outcomes in severe ARDS but may increase risk of ICH and impede cerebral venous drainage.

Physiology

Veno-venous ECMO can improve oxygenation in severely refractory ARDS cases with preserved cardiac function(26). The CESAR trial(101) reported that patients referred to a specialty ECMO

center had higher survival rates with decreased 6-month disability. The EOLIA trial did not replicate these findings, but numerous secondary endpoints demonstrated promise, including reduced treatment failure at 60 days, PP and renal replacement therapy.

Theoretical risk in sABI:

ECMO therapy poses serious potential complications for sABI patients, including hemorrhage, ischemic stroke, air emboli, hypoperfusion, and elevated ICPs(102). Large venous cannulas, often placed in the internal jugular veins, may impede venous drainage. Additionally, the optimal CPP target in sABI patients on ECMO is unknown.

Evidence:

Neurologic complications include hemorrhage, ischemia, impaired cerebral venous drainage, and catheter-associated infection, among others(102). While ECMO is an important salvage therapy in patients with ARDS, sABI patients are usually not considered ECMO candidates. However, novel technology eliminating the need for anticoagulation exists and has been used in trauma patients(103, 104). Case reports have indicated success in using modified anticoagulation protocols in severe TBI patients undergoing ECMO for ARDS. Similarly, decompressive craniectomy has been performed while on ECMO with moderate-to-good outcome(102). Still, acquired coagulopathy and risk of spontaneous intracranial hemorrhage exists on ECMO(102).

Summary:

ECMO may be used in selected patients with sABI. Technology and approaches eliminating or reducing anticoagulation, such as pumpless extracorporeal lung assist devices or femoral cannulation to ensure cerebral venous drainage, enable ECMO to be considered as a more accessible treatment option in sABI patients(105). Multiple case series support their use by showing optimal ventilation and oxygenation while maintaining CPP and avoiding IH(105).

Patient scenarios

Here, we present hypothetical case scenarios highlighting challenges of sABI and ARDS co-management based on real patients, to exemplify co-management challenges and approaches.

Case Presentation 1

24-year-old man presented after falling off a cliff, with severe TBI and a C1 arch fracture requiring a cervical collar.

Neurologic Management:

ICP treatment: An intraparenchymal ICP monitor was placed for a GCS of 4 and compressed cisterns on CT, he subsequently required frequent HT therapy. Sedation was titrated to RASS -5, an extraventricular drain (EVD) was placed on HD 3 and intermittently opened for CSF diversion. Paralytics and pentobarbital were added on HD 4 due to refractory IH. He required vasopressors with an elevated MAP goal of ≥75 to maintain CPP. By HD 7, no further ICP treatments were required.

Pulmonary Management:

On HD 4, he developed septic shock and worsening hypoxemic respiratory failure due to Staphylococcus *aureus* pneumonia, with progressive bilateral opacities on CXR.

ARDS Treatment:

LTVMV was initiated but led to permissive hypercapnia (PCO2 50s) which subsequently increased ICPs. Increasing TVs back to 7cc/kg was not tolerated due to elevated static pressures. Sedation and paralysis were initially started for elevated ICPs, but also helped achieve vent synchrony. Increasing PEEP to 16 improved oxygenation but resulted in refractory ICP elevations. On HD 5, he was proned for 3 days. The spine team was at the bedside during the proning, a soft massage pillow was placed under his shoulders so the cervical collar could remain.

ICPs transiently rose to the 40s during the first proning but decreased after treatment with HT. Reverse Trendelenburg and the addition of pillows under chest and hips to relieve abdominal pressure further improved his ICP. Prior to subsequent proning, HT was given and 20 cc of CSF

were drained from his EVD, no further ICP elevations were noted. Hypoxemia and hypercapnia improved substantially with proning.

Teaching Points:

- Hypercapnea due to LTVMV can result in increased ICPs, resulting in the need to further escalate other ARDS treatments.
- Increased PEEP can result in ICP spikes.
- To maintain CPP, vasopressors may be required to meet adjusted MAP goals.
- Proning may be feasible in patients with spine injury, assessment of cervical spine stability and risks of proning should be assessed in consultation with the spine team.
- Proning may be feasible in patients with elevated ICPs and ICP monitors. Increased ICPs may be observed during proning and can be mitigated with conventional interventions for IH and positioning maneuvers.

Case Presentation 2

26-year-old man presented after a high-speed motorcycle crash, with severe TBI, multiple rib fractures, pulmonary contusions, and unstable open pelvis fracture requiring emergent external fixation. He required massive blood transfusions on admission, and internal iliac embolization followed by external fixation of his pelvis.

Neurologic Management:

ICP Treatment: A parenchymal intracranial pressure and brain tissue oxygen monitor was placed on HD1 for a GCS of 3. ICPs were treated with HT, deep sedation, and paralysis.

Pulmonary Management:

On HD3, he became progressively hypoxemic, presumed due to worsening pulmonary contusions and/or TRALI. Of note, his brain tissue oxygen measures decreased to <20 mmHg on HD 4.

ARDS Treatment: LTVMV with PEEP titration was initiated in addition to deep sedation, paralysis and inhaled epoprostenol. On HD 5, following multidisciplinary conversations, veno-venous (VV) ECMO was initiated given his persistent hypoxemia (including brain tissue hypoxia), and inability to prone due to pelvic fractures. Systemic anticoagulation was deferred due to concerns his large frontal hemorrhagic contusions would blossom. ECMO support was provided for 7 days during which no further ICP treatment was needed. Contusions remained stable on head CT.

Teaching Points:

- ECMO can be utilized in patients with concurrent sABI and ARDS, with appropriate modifications
- Femoral-femoral cannulation circumvents the risk of cerebral venous drainage impedance that may occur with internal jugular cannulation, despite the higher risk of recirculation.
- Use of VV-ECMO for >7 days without systemic anticoagulation using modern, heparin-bonded circuits have been successfully reported and should be considered in cases of concurrent sABI and ARDS.

Special Considerations in the COVID-19 era

Interactions between sABI and ARDS are complex. Prevalence of ARDS is on the rise due to COVID and given the neurological dysfunctions associated with COVID(5), clinicians may have to frequently treat these coexistent pathologies . The main goals in managing these patients are adequate oxygenation and perfusion while avoiding secondary end-organ injury. Understanding which treatments are safe or need modification is critical to optimizing care, particularly given the potential benefit of early proning in COVID patients(106, 107). There are few, if any, trials directly addressing concurrent management of patients with both ARDS and sABI. A recent international expert consensus panel for the European Society Of Intensive Care Medicine (ESICM) on mechanical ventilation in acute brain injury emphasized that evidence is largely lacking for this population, highlighting the need for further research in this area(40).

Our current recommendations are extrapolated based on available data and expert opinion. By increasing utilization of invasive and non-invasive monitoring devices that directly measure brain and lung physiology we can titrate treatment strategies to individualized targets(18, 108, 109). Prospective observational studies, like the newly enrolling VENTIBRAIN study (NCT04459884), may help inform future guidance and prospective clinical trials. Thoughtful multi-specialty discussions optimizing these targets are paramount to maximizing good outcomes.

Table 1: Brain-Lung conflict and recommendations based on current literature review.

Lung-Focused ARDS Therapy	Brain-Focused ABI Therapy	Recommendation
- Low tidal volume mechanical ventilation with permissive hypercarbia	- Avoid hypercarbia/ hypocarbia - Avoid hypoxemia	- Individualized P_aCO_2 and P_aO_2 targets based on ICP and brain tissue oxygenation monitoring - If cerebral monitoring unavailable, goal normocarbia and P_aO_2 >110 mmHg
- High PEEP	- Maximize cerebral venous drainage and CPP	- Ideally maintain PEEP ≤12 cmH_20 - Consider PEEP titration based on ICP monitoring
- Recruitment maneuvers	- Maintain goal CPP	- Avoid recruitment maneuvers using PEEP ≥ 20cm H_20
- Prone positioning	- Maintain HoB elevated - Maximize cerebral venous drainage	- Consider premedication (e.g., hyperosmolar therapy) prior to proning - Reverse Trendelenburg to maintain HoB 30-45° - Midline head position - Avoid ICP monitor dislodgement during repositioning - Alternative strategy: Consider supine chest compression with weights
- ECMO	- Avoid acquired coagulopathy unless indicated for treatment of ABI (e.g., ischemic stroke)	- Avoid jugular cannulation when able - Consider alternative anticoagulation protocols
- Pulmonary vasodilator therapy	- Optimize risk of bleeding	- Limited evidence suggests pulmonary vasodilators are safe and potentially beneficial
- Fluid conservation strategies	- Optimize CPP	- Careful assessment of fluid status and appropriate volume resuscitation
- Sedation and neuromuscular blockade	- Optimize the neurological examination	- Minimal effective doses of sedation and neuromuscular agents should be utilized - Consider alternatives to full neurological assessment (e.g., pupillometry, non-invasive or invasive monitoring)
- Steroids	- Steroids may be harmful in some types of brain injury	- Special consideration to individual patient risk-benefit ratio in patients with ABI

Abbreviations: ABI (acute brain injury); ARDS (acute respiratory distress syndrome); CPP (cerebral perfusion pressure); HoB (head of bed); ECMO (extracorporeal membrane oxygenation); ICP (intracranial pressure); P_aCO_2 (partial pressure arterial carbon dioxide); P_aO_2 (partial pressure arterial oxygen); PEEP (positive end expiratory pressure)

Figure Legend:

Figure 1: Central Nervous System injury pathways to inducing Acute Respiratory Distress Syndrome. Several pathways have been hypothesized to be activated after a brain injury which can subsequently lead to the development or induction of ARDS: 1) Direct or indirect hypothalamic injury, 2) local central nervous system inflammatory response and 3) increase in intracranial pressure(110–113). Abbreviations: CNS=Central nervous system, IL=Interleukin, TNF=Tumor Necrosis Factor, BBB=Blood Brain Barrier, ARDS=Acute Respiratory Distress Syndrome

Figure 2: Summary of potential conflicts in concurrent severe acute brain injury and acute respiratory distress syndrome patients. Treatments targeting improved oxygenation benefit both neurologic and pulmonary physiology. However, other pulmonary treatments may lead to unintended secondary injury on the brain and vice versa.

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References

1. Mascia L: Acute lung injury in patients with severe brain injury: A double hit model. *Neurocrit Care* 2009;

2. Veeravagu A, Chen YR, Ludwig C, et al.: Acute Lung Injury in Patients with Subarachnoid Hemorrhage: A Nationwide Inpatient Sample Study [Internet]. *World Neurosurg* 2014; 82:e235–e241[cited 2020 Nov 18] Available from: https://pubmed.ncbi.nlm.nih.gov/24560705/

3. Holland MC, Mackersie RC, Morabito D, et al.: The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. *J Trauma* 2003;

4. Needham EJ, Chou SHY, Coles AJ, et al.: Neurological Implications of COVID-19 Infections. *Neurocrit Care* 2020;

5. Zubair AS, McAlpine LS, Gardin T, et al.: Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. *JAMA Neurol* 2020;

6. McHugh GS, Engel DC, Butcher I, et al.: Prognostic value of secondary insults in traumatic brain injury: Results from the IMPACT study. *J Neurotrauma* 2007; 24:287–293

7. Elmer J, Hou P, Wilcox SR, et al.: Acute respiratory distress syndrome after spontaneous

intracerebral hemorrhage. *Crit Care Med* 2013; 41:1992–2001

8. Oddo M, Citerio G: ARDS in the brain-injured patient: what's different? *Intensive Care Med* 2016; 42:790–793

9. Mascia L, Zavala E, Bosma K, et al.: High tidal volume is associated with the development of acute lung injury after severe brain injury: An international observational study. *Crit Care Med* 2007; 35:1815–1820

10. Wrigge H, Uhlig U, Zinserling J, et al.: The Effects of Different Ventilatory Settings on Pulmonary and Systemic Inflammatory Responses during Major Surgery. *Anesth Analg* 2004; 98:775–781

11. Brower RG, Matthay MA, Morris A, et al.: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308

12. Slutsky A, Ranieri M: Ventilator-Induced Lung Injury. *N Engl J Med* 2014; 369; 22:2126–2162

13. Brain Taruma Foundation., American Association of Neurological surgeons., Congress of Neurological Surgeons. JSe on N and CC, Bratton S, Chestnut R, et al.: Guidelines for the Manageent of Severe Traumatic Brain Injury. IX. Cerebral perfusion thresholds. *J Neurotrauma* 2007; 24:S59-64

14. Ropper AH: Hyperosmolar Therapy for Raised Intracranial Pressure [Internet]. *N Engl J Med* 2012; 367:746–752Available from: http://dx.doi.org/10.1056/nejmct1206321

15. Godoy DA, Seifi A, Garza D, et al.: Hyperventilation therapy for control of posttraumatic intracranial hypertension. *Front Neurol* 2017;

16. Carney N, Totten AM, O'Reilly C, et al.: Guidelines for the Management of Severe

Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; 80:6–15

17. Cook AM, Morgan Jones G, Hawryluk GWJ, et al.: Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients [Internet]. *Neurocrit Care* 2020; 32:647–666Available from: https://pubmed.ncbi.nlm.nih.gov/32227294

18. Okonkwo DO, Shutter LA, Moore C, et al.: Brain oxygen optimization in severe traumatic brain injury phase-II: A phase II randomized trial [Internet]. *Crit Care Med* 2017; 45:1907–1914[cited 2020 Sep 24] Available from: /pmc/articles/PMC5679063/?report=abstract

19. Group TI-RI and the A and NZICSCT: Conservative Oxygen Therapy during Mechanical Ventilation in the ICU [Internet]. *https://doi.org/101056/NEJMoa1903297* 2019; 382:989–998[cited 2021 Jul 6] Available from: https://www.nejm.org/doi/10.1056/NEJMoa1903297

20. Schjørring OL, Klitgaard TL, Perner A, et al.: Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure [Internet]. *https://doi.org/101056/NEJMoa2032510* 2021; 384:1301–1311[cited 2021 Jul 6] Available from: https://www.nejm.org/doi/10.1056/NEJMoa2032510

21. Davis DP, Meade W, Sise MJ, et al.: Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury [Internet]. *J Neurotrauma* 2009; 26:2217–2223[cited 2020 Nov 18] Available from: https://pubmed.ncbi.nlm.nih.gov/19811093/

22. Picetti E, Pelosi P, Taccone FS, et al.: VENTILatOry strategies in patients with severe traumatic brain injury: the VENTILO Survey of the European Society of Intensive Care Medicine (ESICM).

23. Brower RG, Lanken PN, MacIntyre N, et al.: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;

24. Schramm P, Closhen D, Felkel M, et al.: Influence of PEEP on cerebral blood flow and cerebrovascular autoregulation in patients with acute respiratory distress syndrome. *J Neurosurg Anesthesiol* 2013;

25. Rozet I, Domino KB: Respiratory care. *Best Pract Res Clin Anaesthesiol* 2007;

26. Modock J: Complex care: Ventilation management when brain injury and acute lung injury coexist. *J Neurosci Nurs* 2014;

27. Sahetya SK, Goligher EC, Brower RG: Setting positive end-expiratory pressure in acute respiratory distress syndrome [Internet]. *Am J Respir Crit Care Med* 2017; 195:1429–1438[cited 2020 Aug 20] Available from: http://www.atsjournals.org/doi/10.1164/rccm.201610-2035CI

28. Amato MBP, Maureen D, Meadle O: Driving pressure and survival in the ARDS. *New Engl J Med* 2015;

29. Huseby JS, Luce JM, Cary JM, et al.: Effects of positive end-expiratory pressure on intracranial pressure in dogs with intracranial hypertension. *J Neurosurg* 1981; 55:704–707

30. Huseby JS, Pavlin EG, Butler J: Effect of positive end-expiratory pressure on intracranial pressure in dogs. *J Appl Physiol Respir Environ Exerc Physiol* 1978; 44:25–27

31. Luce JM, Huseby JS, Kirk W, et al.: A Starling resistor regulates cerebral venous outflow in dogs. *J Appl Physiol Respir Environ Exerc Physiol* 1982; 53:1496–1503

32. Lowe GJ, Ferguson ND: Lung-protective ventilation in neurosurgical patients. *Curr Opin Crit Care* 2006;

33. Rosner MJ, Rosner SD, Johnson AH: Cerebral perfusion pressure: Management protocol and clinical results. *J Neurosurg* 1995; 83:949–962

34. Doblar DD, Santiago T V., Kahn AU, et al.: The effect of positive end-expiratory pressure ventilation (PEEP) on cerebral blood flow and cerebrospinal fluid pressure in goats. *Anesthesiology* 1981; 55:244–250

35. Videtta W, Villarejo F, Cohen M, et al.: Effects of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. *Acta Neurochir Suppl* 2002; 81:93–97

36. McGuire G, Crossley D, Richards J, et al.: Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. *Crit Care Med* 1997; 25:1059–1062

37. Caricato A, Conti G, Della Corte F, et al.: Effects of PEEP on the intracranial system of patients with head injury and subarachnoid hemorrhage: The role of respiratory system compliance. *J Trauma - Inj Infect Crit Care* 2005;

38. Huynh T, Messer M, Sing RF, et al.: Positive end-expiratory pressure alters intracranial and cerebral perfusion pressure in severe traumatic brain injury. *J Trauma - Inj Infect Crit Care* 2002;

39. Georgiadis D, Schwarz S, Baumgartner RW, et al.: Influence of Positive End-Expiratory Pressure on Intracranial Pressure and Cerebral Perfusion Pressure in Patients With Acute Stroke. *Stroke* 2001; 32:2088–2092

40. Robba C, Poole D, McNett M, et al.: Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus [Internet]. *Intensive Care Med* 2020; 46:2397–2410Available from: https://doi.org/10.1007/s00134-020-06283-0

41. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et al.: Effect of lung recruitment and titrated

Positive End-Expiratory Pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome - A randomized clinical trial [Internet]. *JAMA - J Am Med Assoc* 2017; 318:1335–1345[cited 2020 Aug 20] Available from: https://jamanetwork.com/

42. Nemer SN, Caldeira JB, Azeredo LM, et al.: Alveolar recruitment maneuver in patients with subarachnoid hemorrhage and acute respiratory distress syndrome: A comparison of 2 approaches. *J Crit Care* 2011;

43. De Rosa S, Franchi P, Mancino A, et al.: Impact of positive end expiratory pressure on cerebral hemodynamic in paediatric patients with post-traumatic brain swelling treated by surgical decompression. *PLoS One* 2018;

44. Siobal MS, Kallet RH, Pittet JF, et al.: Description and evaluation of a delivery system for aerosolized prostacyclin. *Respir Care* 2003;

45. Cavallini L, Coassin M, Borean A, et al.: Prostacyclin and sodium nitroprusside inhibit the activity of the platelet inositol 1,4,5-trisphosphate receptor and promote its phosphorylation. *J Biol Chem* 1996;

46. Menitove JE, Frenzke M, Aster RH: Use of prostacyclin to inhibit activation of platelets during preparation of platelet concentrates. *Transfusion* 1984;

47. Papadimos TJ, Medhkour A, Yermal S: Successful use of inhaled nitric oxide to decrease intracranial pressure in a patient with severe traumatic brain injury complicated by acute respiratory distress syndrome: a role for an anti-inflammatory mechanism? *Scand J Trauma Resusc Emerg Med* 2009;

48. Vanhoonacker M, Roeseler J, Hantson P: Reciprocal influence of refractory hypoxemia and high intracranial pressure on the postoperative management of an urgent neurosurgical procedure. *Respir Care* 2012;

49. Khan MF, Azfar MF, Khurshid SM: The role of inhaled nitric oxide beyond ARDS. *Indian J Crit Care Med* 2014;

50. Gritti P, Lanterna LA, Re M, et al.: The use of inhaled nitric oxide and prone position in an ARDS patient with severe traumatic brain injury during spine stabilization. *J Anesth* 2013;

51. Weed LH, McKibben PS: PRESSURE CHANGES IN THE CEREBRO-SPINAL FLUID FOLLOWING INTRAVENOUS INJECTION OF SOLUTIONS OF VARIOUS CONCENTRATIONS [Internet]. *Am J Physiol Content* 1919; 48:512–530Available from: http://dx.doi.org/10.1152/ajplegacy.1919.48.4.512

52. Changa AR, Czeisler BM, Lord AS: Management of Elevated Intracranial Pressure: a Review [Internet]. *Curr Neurol Neurosci Rep* 2019; 19Available from: http://dx.doi.org/10.1007/s11910-019-1010-3

53. Wiedemann HP, Wheeler AP, Bernard GR, et al.: Comparison of Two Fluid-Management Strategies in Acute Lung Injury [Internet]. *N Engl J Med* 2006; 354:2564–2575[cited 2020 Aug 20] Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa062200

54. Chesnut RM, Chesnut RM, Marshall LF, et al.: The role of secondary brain injury in determining outcome from severe head injury [Internet]. *J Trauma - Inj Infect Crit Care* 1993; 34:216[cited 2020 Sep 25] Available from: https://pubmed.ncbi.nlm.nih.gov/8459458/

55. Lennihan L, Mayer SA, Fink ME, et al.: Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: A randomized controlled trial. *Stroke* 2000; 31:383–391

56. Solomon RA, Fink ME, Lennihan L: Prophylactic Volume Expansion Therapy for the Prevention of Delayed Cerebral Ischemia After Early Aneurysm Surgery: Results of a

Preliminary Trial. *Arch Neurol* 1988; 45:325–332

57. van der Jagt M: Fluid management of the neurological patient: A concise review [Internet]. *Crit Care* 2016; 20:1–11Available from: http://dx.doi.org/10.1186/s13054-016-1309-2

58. Shah FA, Girard TD, Yende S: Limiting sedation for patients with acute respiratory distress syndrome-time to wake up [Internet]. *Curr Opin Crit Care* 2017; 23:45–51[cited 2020 Aug 20] Available from: /pmc/articles/PMC5729753/?report=abstract

59. Papazian L, Forel JM, Gacouin A, et al.: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;

60. Moss M, Huang DT, Brower RG, et al.: Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome [Internet]. *N Engl J Med* 2019; 380:1997–2008[cited 2020 Aug 20] Available from: http://www.nejm.org/doi/10.1056/NEJMoa1901686

61. Alnemari AM, Krafcik BM, Mansour TR, et al.: A Comparison of Pharmacologic Therapeutic Agents Used for the Reduction of Intracranial Pressure After Traumatic Brain Injury [Internet]. *World Neurosurg* 2017; 106:509–528Available from: http://dx.doi.org/10.1016/j.wneu.2017.07.009

62. Freeman WD: Management of Intracranial Pressure [Internet]. *Contin Lifelong Learn Neurol* 2015; 21:1299–1323Available from: http://dx.doi.org/10.1212/con.0000000000000235

63. Raised intracranial pressure: What it is and how to recognise it | Roytowski | Continuing Medical Education [Internet]. [cited 2020 Sep 24] Available from: http://www.cmej.org.za/index.php/cmej/article/view/2698/0

64. Steen PA, Michenfelder JD: Cerebral Protection with Barbiturates Relation to Anesthetic

Effect [Internet]. [cited 2020 Sep 29] Available from: http://ahajournals.org

65. I V, N L, G V den B: ICU-acquired weakness [Internet]. *Intensive Care Med* 2020; 46:637–653[cited 2021 Jul 6] Available from: https://pubmed.ncbi.nlm.nih.gov/32076765/

66. Skoglund K, Enblad P, Marklund N: Effects of the neurological wake-up test on intracranial pressure and cerebral perfusion pressure in brain-injured patients [Internet]. *Neurocrit Care* 2009; 11:135–142[cited 2020 Sep 29] Available from: https://pubmed.ncbi.nlm.nih.gov/19644774/

67. Helbok R, Kurtz P, Schmidt MJ, et al.: Effects of the neurological wake-up test on clinical examination, intracranial pressure, brain metabolism and brain tissue oxygenation in severely brain-injured patients [Internet]. *Crit Care* 2012; 16:R226[cited 2020 Sep 29] Available from: /pmc/articles/PMC3672610/?report=abstract

68. Wilson JG, Calfee CS: ARDS Subphenotypes: Understanding a Heterogeneous Syndrome [Internet]. *Crit Care 2020 241* 2020; 24:1–8[cited 2021 Jul 6] Available from: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-2778-x

69. Witt KA, Sandoval KE: Steroids and the Blood–Brain Barrier: Therapeutic Implications. *Adv Pharmacol* 2014; 71:361–390

70. GALICICH JH, FRENCH LA: Use of dexamethasone in the treatment of cerebral edema resulting from brain tumors and brain surgery. *Am Pract Dig Treat* 1961; 12:169–174

71. Muzumdar D, Jhawar S, Goel A: Brain abscess: An overview [Internet]. *Int J Surg* 2011; 9:136–144Available from: http://dx.doi.org/10.1016/j.ijsu.2010.11.005

72. Wijdicks EFM, Sheth KN, Carter BS, et al.: Recommendations for the management of cerebral and cerebellar infarction with swelling: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;

73. Baigent C, Bracken M, Chadwick D, et al.: Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury - outcomes at 6 months. *Lancet* 2005;

74. Villar J, Ferrando C, Martínez D, et al.: Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial [Internet]. *Lancet Respir Med* 2020; 8:267–276[cited 2020 Aug 20] Available from: http://www.thelancet.com/article/S2213260019304175/fulltext

75. Meduri GU, Golden E, Freire AX, et al.: Methylprednisolone infusion in early severe ards: Results of a randomized controlled trial. *Chest* 2007;

76. Steinberg KP, Hudson LD, Goodman RB, et al.: Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome [Internet]. *N Engl J Med* 2006; 354:1671–1684[cited 2020 Aug 20] Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa051693

77. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al.: Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. [Internet]. *JAMA* 2020; [cited 2020 Sep 25] Available from: http://www.ncbi.nlm.nih.gov/pubmed/32876694

78. Group TRC: Dexamethasone in Hospitalized Patients with Covid-19 [Internet]. *https://doi.org/101056/NEJMoa2021436* 2020; 384:693–704[cited 2021 Jul 15] Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2021436

79. Johnson NJ, Luks AM, Glenny RW: Gas exchange in the prone posture [Internet]. *Respir Care* 2018; 62:1097–1110[cited 2020 Aug 20] Available from: http://rc.rcjournal.com/content/62/8/1097

80. Sud S, Friedrich JO, Taccone P, et al.: Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: Systematic review and meta-analysis. *Intensive Care Med* 2010;

81. Guérin C, Reignier J, Richard J-C, et al.: Prone Positioning in Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2013; 368:2159–2168

82. Scholten EL, Beitler JR, Prisk GK, et al.: Treatment of ARDS With Prone Positioning. *Chest* 2017;

83. Roth C, Ferbert A, Deinsberger W, et al.: Does Prone Positioning Increase Intracranial Pressure? A Retrospective Analysis of Patients with Acute Brain Injury and Acute Respiratory Failure. *Neurocrit Care* 2014;

84. Bein T, Kuhr LP, Bele S, et al.: Lung recruitment maneuver in patients with cerebral injury: Effects on intracranial pressure and cerebral metabolism. *Intensive Care Med* 2002;

85. Munshi L, Del Sorbo L, Adhikari NKJ, et al.: Prone position for acute respiratory distress syndrome: A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017;

86. Blanch L, Mancebo J, Perez M, et al.: Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. *Intensive Care Med* 1997; 23:1033–1039

87. Johannigman JA, Davis K, Miller SL, et al.: Prone positioning for acute respiratory distress syndrome in the surgical intensive care unit: Who, when, and how long? *Surgery* 2000; 128:708–716

88. Magnaes B: Body position and cerebrospinal fluid pressure [Internet]. *J Neurosurg* 1976; 44:698–705Available from: http://dx.doi.org/10.3171/jns.1976.44.6.0698

89. Magnaes B: Body Position and Cerebrospinal Fluid Pressure [Internet]. *Neurobiol Cerebrospinal Fluid 2* 1983; 629–642Available from: http://dx.doi.org/10.1007/978-1-4615-9269-3_39

90. Fan J-Y: Effect of Backrest Position on Intracranial Pressure and Cerebral Perfusion Pressure in Individuals with Brain Injury [Internet]. *J Neurosci Nurs* 2004; 36:278–288Available from: http://dx.doi.org/10.1097/01376517-200410000-00007

91. Kenning JA, Toutant SM, Saunders RL: Upright patient positioning in the management of intracranial hypertension [Internet]. *Surg Neurol* 1981; 15:148–152Available from: http://dx.doi.org/10.1016/0090-3019(81)90037-9

92. Hawryluk GWJ, Aguilera S, Buki A, et al.: A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). In: Intensive Care Medicine. Springer; 2019. p. 1783–1794.

93. Ng I, Lim J, Wong HB, et al.: Effects of Head Posture on Cerebral Hemodynamics: Its Influences on Intracranial Pressure, Cerebral Perfusion Pressure, and Cerebral Oxygenation [Internet]. *Neurosurgery* 2004; 54:593–598[cited 2020 Sep 24] Available from: https://pubmed.ncbi.nlm.nih.gov/15028132/

94. Anderson CS, Olavarría V V.: Head Positioning in Acute Stroke [Internet]. *Stroke* 2019; 50:224–228[cited 2020 Nov 24] Available from: https://www.ahajournals.org/doi/10.1161/STROKEAHA.118.020087

95. Reinprecht A, Greher M, Wolfsberger S, et al.: Prone position in subarachnoid hemorrhage patients with acute respiratory distress syndrome: Effects on cerebral tissue oxygenation and intracranial pressure. *Crit Care Med* 2003; 31:1831–1838

96. Beuret P, Carton MJ, Nourdine K, et al.: Prone position as prevention of lung injury in comatose patients: A prospective, randomized, controlled study. *Intensive Care Med* 2002; 28:564–569

97. Thelandersson A, Cider Å, Nellgård B: Prone position in mechanically ventilated patients with reduced intracranial compliance. *Acta Anaesthesiol Scand* 2006; 50:937–941

98. Nekludov M, Bellander BM, Mure M: Oxygenation and cerebral perfusion pressure improved in the prone position. *Acta Anaesthesiol Scand* 2006; 50:932–936

99. Kayani A s., Feldman J p.: Prone ventilation in a patient with traumatic brain injury, bifrontal craniectomy and intracranial hypertension. *Trauma* 2015;

100. ALTERPRONE Clinical Trial [Internet]. Available from: https://clinicaltrials.gov/ct2/show/NCT03719937

101. Peek GJ, Mugford M, Tiruvoipati R, et al.: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;

102. Sutter R, Tisljar K, Marsch S: Acute Neurologic Complications During Extracorporeal Membrane Oxygenation: A Systematic Review [Internet]. *Crit Care Med* 2018; 46:1506–1513[cited 2021 Jul 6] Available from: https://pubmed.ncbi.nlm.nih.gov/29782356/

103. Kurihara C, Walter JM, Karim A, et al.: Feasibility of Venovenous Extracorporeal Membrane Oxygenation Without Systemic Anticoagulation. In: Annals of Thoracic Surgery. Elsevier USA; 2020. p. 1209–1215.

104. Juthani B, Hilaire C ST., Auvil B, et al.: Outcomes of Adult Venovenous Extracorporeal Membrane Oxygenation Patients without Anticoagulation: A Retrospective Review at a Tertiary Level Referral Center [Internet]. *J Am Coll Surg* 2016; 223:S24[cited 2020 Sep

25] Available from: http://www.journalacs.org/article/S1072751516303155/fulltext

105. Munoz-Bendix C, Beseoglu K, Kram R: Extracorporeal decarboxylation in patients with severe traumatic brain injury and ARDS enables effective control of intracranial pressure. *Crit Care* 2015;

106. Paul V, Patel S, Royse M, et al.: Proning in Non-Intubated (PINI) in Times of COVID-19: Case Series and a Review. *J Intensive Care Med* 2020;

107. Caputo ND, Strayer RJ, Levitan R: Early Self-Proning in Awake, Non-intubated Patients in the Emergency Department: A Single ED's Experience During the COVID-19 Pandemic. *Acad Emerg Med* 2020;

108. Lara LR, Püttgen HA: Multimodality Monitoring in the Neurocritical Care Unit. *Contin Lifelong Learn Neurol* 2018; 24:1776–1788

109. Corradi F, Robba C, Tavazzi G, et al.: Combined lung and brain ultrasonography for an individualized "brain-protective ventilation strategy" in neurocritical care patients with challenging ventilation needs [Internet]. *Crit Ultrasound J* 2018; 10[cited 2020 Sep 29] Available from: https://pubmed.ncbi.nlm.nih.gov/30221312/

110. Moss G: Shock, cerebral hypoxia, and pulmonary vascular control: the centrineurogenic etiology of the respiratory distress syndrome. [Internet]. *Bull N Y Acad Med* 1973; 49:689[cited 2021 Jul 6] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1807072/

111. GG de O, MP A: Role of the central nervous system in the adult respiratory distress syndrome [Internet]. *Crit Care Med* 1987; 15:844–849[cited 2021 Jul 6] Available from: https://pubmed.ncbi.nlm.nih.gov/3621959/

112. L B, M Q: Lung-brain cross talk in the critically ill [Internet]. *Intensive Care Med* 2017;

43:557–559[cited 2021 Jul 6] Available from: https://pubmed.ncbi.nlm.nih.gov/27714405/

113. S M, JM C, T G: Brain-lung crosstalk: Implications for neurocritical care patients [Internet]. *World J Crit care Med* 2015; 4:163[cited 2021 Jul 6] Available from: https://pubmed.ncbi.nlm.nih.gov/26261769/